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Research Article

Benefits of Prolonged Anticoagulant Treatment in a Series of Cerebral Venous Thrombosis in Pediatric Patients

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Abstract

Background: Cerebral sinus venous thrombosis (CSVT) is a rare complication in children, usually secondary to an underlying condition. Recent guidelines recommend treating all pediatric patients with CSVT, but also suggest that treatment longer than three months should not be justified in provoked cases in which the risk factor has disappeared.

Methods: Retrospective observational study analyzing data of CSVT in children (1-18 years-old) admitted in a single hospital. Demographic data, clinical presentation, etiology, extension, treatment and outcome were evaluated.

Results: Thirty-one patients had a confirmed CSVT. Sixteen were girls, mean age was 7.3 years (SD 4.39). Sigmoid sinus (n=17) and transverse sinus (n=14) were the most frequent sinuses affected. Multiple sinus thrombosis was found in 20 patients (64.5%). Underlying condition was described in 29 cases: infectious disease (n=20), major head trauma (n=4), chemotherapy (n=3), arteriovenous malformation (n=2). More frequent symptoms were: headache (n= 15), decreased level of consciousness (n=5), seizures (n=3), focal neurological deficit (n=2), papilledema (n=2), diplopia (n=2), vision impairment (n=1), and coma (n=4). All patients received anticoagulant treatment. Complete vein recanalization after 3 months was achieved in 53.3% of the cases. Treatment was prolonged up to 6 months in those patients with partial or no response (n=14). Seven of them improved radiological findings. Complete and partial vein recanalization were reported in 73.3% and 20% of the patients.

Conclusion: Anticoagulation was useful to achieve complete vein recanalization in this series. Extending anticoagulation up to 6 months could be useful to improve outcome of pediatric patients with CSVT in selected cases.

Keywords: Sinus thrombosis; Pediatric; Anticoagulant treatment; Treatment outcome

Background

Cerebral sinus venous thrombosis (CSVT) is a rare condition in pediatric patients (0.7 cases per 100,000 children and year) [1]. Most of them are secondary to well known risk factors: head and neck infections, cranial traumatism, chemotherapy treatment (steroids and asparaginase), inherited or acquired thrombophilia, and hormonal treatment with estrogens [2-4]. Headache and other neurological manifestations as seizures, decreased level of consciousness, or focal neurologic deficits are frequent but unspecific symptoms of CSVT [4,5]. In fact, diagnosis is exclusively radiological: computerized tomography angiography (CT) and/or magnetic resonance imaging angiography (MRI) [2].

Treatment approach to CSVT in pediatric population is still controversial and relies on recommendations with a low level of evidence [6-8]. Anticoagulation reduces thrombus progression, mortality, and recurrence risk with a low rate of hemorrhagic complications [9,10]. Thus, last American Society of Hematology guidelines for management of venous thromboembolism strongly recommends using anticoagulation in children with CSVT without hemorrhage and suggest using it in patients with hemorrhage. The authors also suggest that those patients with a provoked deep venous thrombosis should receive treatment for three months (or less in selected cases) if the risk factor is resolved. Treatment should be longer (6-12 months) in unprovoked cases [7].

Treatment efficacy varies depending on the published series and CSVT etiology. Complete or partial recanalization occurs up to 83% of patients with CSVT secondary to head or neck infections after 3-12 months under anticoagulant treatment [11,12]. However, a recent randomized study of 114 patients with CSVT and different etiologies described a lower recanalization rate after a 3-month period of treatment. Complete or partial sinus recanalization as observed in 78% of the patients treated with rivaroxaban and 64% in those treated with standard anticoagulants [5].

The aim of this study was to evaluate the efficacy of prolonged antithrombotic treatment in a pediatric series of CSVT while describing clinical presentation, radiological findings, and outcome.

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Methods

Observational retrospective study to evaluate the efficacy of antithrombotic treatment in a series of pediatric patients (age 1 month-18 years) diagnosed with CSVT treated in a single tertiary pediatric hospital from January 2011 to December 2021. CSVT diagnosis was based on clinical presentation and confirmed by neuroimaging studies in all cases.

Medical charts were revised to collect: age at diagnosis, gender, family history of thrombosis, clinical presentation, etiology, neuroimaging studies and radiological findings at onset and during follow-up, surgical approach (if needed), anticoagulation treatment (type, dose, duration), laboratory test (including treatment control evaluations), hemorrhage associated to treatment and long-term outcome related to CSVT.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS Statistics, version 27.0). Descriptive statistics included frequencies and percentages for categorical variables and means, standard deviations, confidence intervals, medians, and interquartile ranges for continuous variables. Categorical variables were assessed by Chi2-test and continuous variables by t-test or Mann-Whitney test. p values were considered statistically significant when <0.05.

Results

A total of 31 patients had a confirmed CSVT during the study period. Sixteen were girls and mean age was 7.3 years (SD 4.39). All of them were diagnosed by imaging, CT in 21 cases, MRI in other 10. The most common sites of CSVT were sigmoid sinuses (n=17) and transverse sinuses (n=14). The superior sagittal sinus was affected in seven cases and superior ophthalmic vein in three cases. Of note, internal jugular vein was also thrombosed in eight cases, but no central venous device was associated to this finding. Whereas CSVT involving one sinus occurred in 11 patients (35.5 %), multiple localizations were found in 20 (64.5%). Those patients with CSVT in more than one sinus did not have a higher incidence of intracranial complications as cerebral abscesses or meningitis comparing to those with only one sinus affected.

Twenty-nine cases had an underlying condition: infectious disease (n=20), major head trauma (n=4), chemotherapy during acute lymphoblastic leukemia (ALL) induction phase (n=3), arteriovenous malformation (n=2). CSVT were idiopathic in two patients. Headache was the most frequent symptom (n= 15), followed by decreased level of consciousness (n=5), seizures (n=3), focal neurological deficit (n=2), papilledema (n=2), diplopia (n=2), vision impairment (n=1). Four patients presented with coma (those with major head trauma as risk factor). CSVT was a radiological finding in two patients with mastoiditis.

All patients received anticoagulant initial treatment with low molecular weight heparin (LMWH) (enoxaparin n=27, enoxaparin + acenocoumarin n=4). Anti X activated was evaluated in 50% of the patients. Relevant dose modifications were not necessary in any case. None received thrombolytic therapy. Mastoidectomy and/or cerebral abscess drainage was needed in 17 patients. Of them, seven patients had not started anticoagulant treatment, but ten patients had already received enoxaparin. Anticoagulation was withdrawn before surgery in these cases and reinitiated 24-48 hours later. Five patients had an associated hemorrhage at diagnosis (those with major head trauma and a patient with mastoiditis and cerebral abscess). Enoxaparin was administered at low doses (0.5 mg/kg every 12 hours) during the first

Table 1: CSVT global outcome after 3 and 6 months of treatment according to etiology, thrombosis extension and treatment characteristics.

	Recanalization outcome after 3 months of treatment			Patients with treatment continuation	Recanalization outcome in patients with prolong treatment up to 6 months		
	Complete n (%)	Partial n (%)	Absence n (%)		Complete n (%)	Partial n (%)	Absence n (%)
Etiology							
Infectious disease (n=20)	11 (55%)	8 (40%)	1 (5%)*	9	5 (55.5%)	4 (44.5%)	-
Major head trauma (n=3)	3 (100%)	-	-	-	-	-	-
Chemotherapy (n=3)	2 (66.6%)	1 (33.3%)	-	1	1 (100%)	-	-
A-V malformation (n=2)	-	-	2 (100%)	2	-	1 (50%)	1 (50%)
Idiopathic (n=2)	-	2 (100%)	-	2	-	2 (100%)	-
Extension							
Only one SV affected (n=19)	11 (57.9%)	6 (31.6%)	2 (10.5%)	8	3 (37.5%)	4 (50%)	1 (12.5%)
More than one SV affected (n=11)	5 (45.5%)	5 (45.5%)	1 (9.1%)	6	3 (50%)	3 (50%)	-
LMWH withdrawal/delayed due to surgery necessity in patients with underlying infectious disease							
Yes (n=17)	8 (47.1%)	8 (47%)	1 (5.9%)	9	5 (55.5%)	4 (44.5%)	-
No (n=3)	3 (100%)	-	-	-	-	-	-
Initial LMWH dose							
Anticoagulant dose (n=26)	13 (50%)	10 (38.5%)	3 (11.5%)	13	5 (38.5%)	7 (53.8%)	1 (7.7%)
Prophylactic dose (n=4)	3 (75%)	1 (25%)	-	1	1 (100%)	-	-

A-V: Arteriovenous. The total number of patients is 30 as follow-up was lost in one patient. *A patient with no recanalization after 3-month period treatment achieves a complete recanalization 3 months later.

7-14 days of treatment in four patients and during 6 weeks in another one. No hemorrhagic events related to treatment were described in any patient.

Anticoagulation efficacy was evaluated in thirty patients as a boy with a CSVT secondary to major head trauma was referred to another hospital and follow-up was lost. Risk factors disappeared or improved in all cases except in those patients under chemotherapy for ALL. Anticoagulation was stopped after three months of treatment in those patients with complete sinus recanalization (n=16; 53.3%). However, patients with partial or without recanalization (n=14; 46.6%) continued anticoagulants administration up to a total of six months. Seven of them improved their radiological results. In summary, complete recanalization after three or six months of treatment was achieved in 73.3% of the patients and partial in 23.3%. Treatment only failed in one case. Table 1 resumes CSVT outcome after 3 and 6 months of anticoagulant administration according to etiology, thrombosis extension and treatment characteristics. Statistical significant differences between groups were not found.

After treatment completion, recurrence has not been reported in any case. Prophylactic LMWH was administered during asparaginase re-exposures in those patients under treatment for ALL. Inherited thrombophilia was evaluated in idiopathic CSVT and secondary to chemotherapy treatment during ALL with no findings.

Discussion

This study describes a series of pediatric patients with provoked and unprovoked CSVT in whom a prolonged treatment up to six months allowed an improvement of sinus recanalization in seven out of 14 patients. This was seen independently of its etiology or thrombosis extension.

According to literature, the rate of CSVT secondary to an underlying condition was high and infections in head and neck were the most frequent etiology in this series. As previously reported, symptoms were unspecific. Whereas headache and neurological symptoms as seizures and focal neurological deficit were the most common clinical findings, diplopia, visual impairment, and papilledema were less reported [2,3,5,9,13]. Radiological findings showed that sigmoid and transverse sinuses were the most common localizations of thrombosis, likely related to the proximity of mastoids, as otitis media and mastoiditis were the most frequent underlying conditions in our series [3,5,13]. A high proportion of patients (64.5%) had more than one affected sinus. This has been related to other intracranial complications as cerebral abscess or meningitis, and a worse outcome [9], but we did not find this relationship.

Following recommendations of main international guidelines, our patients received prompt anticoagulant treatment with LMWH [7], including those with an associated hemorrhage. We faced this complication in five patients, in whom, as stated in American College of chest physicians antithrombotic therapy recommendations of 2012 [6], lower LMWH was started initially. However, this fact did not seem to affect their outcome. Another associated problem was the need of surgery after diagnosis, as there is a potential risk of thrombus extension when treatment is withheld or postponed [10]. Mastoidectomy and/or cerebral abscess drainage was performed in 17 patients, but complete resolution rate after three months of anticoagulant treatment was similar to what is described in literature [5]. Of note, anticoagulation seemed to be safe as hemorrhagic events associated to treatment were not reported in any patient.

After a 3-month treatment period, Connor et al. [5] reported that 25% of the patients under treatment with rivaroxaban and 15% of patients who had received standard anticoagulation achieved a complete sinus recanalization. This rate was higher in our series (53.3%) but patients with otogenic CSVT were likely overrepresented, and we did not included newborns, two facts that could have affected this outcome.

Contrary to recent international recommendations [7], we decided to maintain anticoagulation in those cases with partial or no recanalization after a 3-month treatment period despite the provoking factor had been resolved. This strategy allowed improving outcome in seven out 14 cases, an important number of patients.

This retrospective study has some limitations. As recruitment period was very long, international and local treatment recommendations changed during this time, and this could have affected to some collected data. Other limitations were the lack of children <1 month-old and a high rate of CSVT secondary to infection, and that long-term outcomes were not evaluated.

In summary, anticoagulation treatment seemed to be safe and useful in CSVT pediatric patients. Complete response after 3 months of treatment was high, but we speculate that some patients need to continue treatment even though the provoking factor had disappeared. This strategy allowed a complete and partial vein recanalization of 73.3% and 20% in our patients. International and multicenter studies would be helpful to draw further conclusions in this topic.

References

1. deVeber G, Andrew M, Adams C, Bjornson B, Booth F, Buckley DJ, et al. Cerebral sinovenous thrombosis in children. The New England journal of medicine. 2001; 345: 417-423.

2. Lazzareschi I, Curatola A, Gatto A, Maellaro F, Frassanito P, Basso M, et al. Diagnosis and management of cerebral venous sinus thrombosis in children: a single-center retrospective analysis. Child's nervous system ChNS: Official journal of the International Society for Pediatric Neurosurgery. 2021; 37: 153-160.

3. Grunt S, Wingeier K, Wehrli E, Boltshauser E, Capone A, Fluss J, et al. Cerebral sinus venous thrombosis in Swiss children. Developmental medicine and child neurology. 2010; 52: 1145-1150.

4. Wasay M, Bakshi R, Bobustuc G, Kojan S, Sheikh Z, Dai A, et al. Cerebral venous thrombosis: analysis of a multicenter cohort from the United States. Journal of stroke and cerebrovascular diseases: the official journal of National Stroke Association. 2008; 17: 49-54.

5. Connor P, Sánchez van Kammen M, Lensing AWA, Chalmers E, Kállay K, Hege K, et al. Safety and efficacy of rivaroxaban in pediatric cerebral venous thrombosis (EINSTEIN-Jr. CVT). Blood advances. 2020; 4: 6250-6258.

6. Monagle P, Chan AKC, Goldenberg NA, Ichord RN, Journeycake JM, Nowak-Göttl U, et al. Antithrombotic therapy in neonates and children: Antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. Chest. 2012; 141: e737S-e801S.

7. Monagle P, Cuello CA, Augustine C, Bonduel M, Brandão LR, Capman T, et al. American Society of Hematology 2018 Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism. Blood advances. 2018; 2: 3292-3316.

8. Chalmers E, Ganesen V, Liesner R, Maroo S, Nokes T, Saunders D, et al. Guideline on the investigation, management and prevention of venous thrombosis in children. British journal of haematology. 2011; 154: 196-207.

9. Coutinho J, de Bruijn SF, deVeber G, Stam J. Anticoagulation for cerebral venous sinus thrombosis. Cochrane Database of Systematic Reviews. 2011; 2011: CD002005.

10. Kenet G, Kirkham F, Niederstadt T, Heinecke A, Saunders D, Stoll M, et al. Risk factors for recurrent venous thromboembolism in the European collaborative paediatric database on cerebral venous thrombosis: a multicentre cohort study. The Lancet Neurology. 2007; 6: 595-603.

11. Wong BYW, Hickman S, Richards M, Jassar P, Wilson T. Management of paediatric otogenic cerebral venous sinus thrombosis: a systematic review. Clinical otolaryngology: official journal of ENT-UK; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery. 2015; 40: 704-714.

12. Coutinho G, Júlio S, Matos R, Santos M, Spratley J. Otogenic cerebral venous thrombosis in children: A review of 16 consecutive cases. International journal of pediatric otorhinolaryngology. 2018; 113: 177-181.

13. Ozcan A, Canpolat M, Doganay S, Unal E, Karakukcu M, Ozdemir MA, et al. Cerebral Sinus Venous Thrombosis and Prothrombotic Risk Factors in Children: A Single-Center Experience From Turkey. Journal of pediatric hematology/oncology. 2018; 40: e369-372.